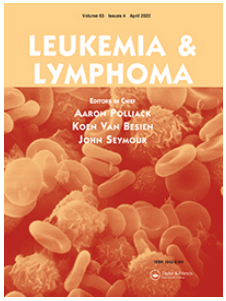

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Letermovir vs. high-dose valacyclovir for cytomegalovirus prophylaxis following haploidentical or mismatched unrelated donor allogeneic hematopoietic cell transplantation receiving post-transplant cyclophosphamide

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ORIGINAL ARTICLE

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Letermovir vs. high-dose valacyclovir for cytomegalovirus prophylaxis following haploidentical or mismatched unrelated donor allogeneic hematopoietic cell transplantation receiving post-transplant cyclophosphamide

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ABSTRACT

Patients undergoing haploidentical or mismatched unrelated donor (haplo/MMUD) allogeneic hematopoietic cell transplantation (alloHCT) receiving post-transplant cyclophosphamide (PTCy) are at high risk of cytomegalovirus (CMV) infection. Experience with letermovir (LET) in this population is limited. This single center retrospective cohort study compared CMV and transplant outcomes between LET and a historical control with high-dose valacyclovir (HDV) prophylaxis in adults undergoing haplo/MMUD alloHCT. Thirty-eight CMV seropositive patients were included, 19 in each arm. LET reduced the incidence of CMV infection (5% vs. 53%, RR 0.01, 95% CI 0.014–0.71, $p = .001$) and need for CMV treatment by day +100 (5% vs. 37%, RR 0.14, 95% CI 0.18–0.99, $p = .017$) compared to HDV. Median CMV event-free-survival was improved with LET (not reached vs. 80 days, HR 0.114, 95% CI 0.07–0.61, $p = .004$). These data support the efficacy of LET in alternative donor transplants.

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Letermovir; valacyclovir; cytomegalovirus; haploidentical; post-transplant cyclophosphamide; prophylaxis

Introduction

Cytomegalovirus (CMV) infection is associated with increased mortality following allogeneic hematopoietic cell transplantation (alloHCT) [1–3]. Patients undergoing haploidentical (haplo) and mismatched unrelated donor (MMUD) alloHCT often receive post-transplant cyclophosphamide (PTCy) graft vs. host disease (GVHD) prophylaxis which is associated with an increased risk of CMV infection [3–6], particularly early post alloHCT prior to viral specific T-cell recovery [7]. Patients at high risk for CMV infection may be candidates for CMV prophylaxis. The utility of (val)ganciclovir prophylaxis is limited by significant myelosuppression [8–10], with similar outcomes observed with preemptive therapy [11]. A less myelosuppressive agent such as high-dose valacyclovir (HDV) 2 g by mouth (PO) every 6–8 h, with or without pre-alloHCT ganciclovir (GCV), demonstrated low rates of CMV infection; however, haplo alloHCTs were not included and clinical use of PTCy was not widespread at the time [12–15]. Unfortunately, use of HDV is complicated by high tablet burden and insurance coverage restrictions. The CMV terminase complex inhibitor letermovir (LET) demonstrated a reduction in clinically significant CMV infection (csCMVi) at 14 and 24 weeks vs. placebo following alloHCT; however, haplo and MMUD alloHCTs receiving PTCy had limited representation (approximately 14% each) [16]. Small single center series have reported the use of LET following haplo alloHCT; however, comparisons to an active control, such as HDV, remain limited [17,18].

Prior to February 2019, HDV was our institutional standard for CMV prophylaxis following haplo alloHCT or alloHCT otherwise receiving PTCy. We anecdotally observed a high incidence of CMV infection and changed to LET. This study aimed to compare CMV and

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transplant outcomes between HDV and LET for patients undergoing haplo or MMUD alloHCT with PTCy.

Methods

This is a single center retrospective cohort study of CMV seropositive adults (age ≥18 years) who underwent haplo or MMUD alloHCT with PTCy between February 2013 and May 2020 at the Hospital of the University of Pennsylvania. Myeloablative conditioning consisted of fludarabine and total body irradiation [19] or busulfan and cyclophosphamide [20]. Reduced intensity conditioning consisted of fludarabine, cyclophosphamide, and low-dose total-body irradiation [21]. From February 2013 to January 2019, patients received HDV 2 g PO every 8 h from day +10 until at least day +100. From February 2019 to May 2020, patients received LET 480 mg PO or intravenous daily from day +10 until at least day +100. Occasionally antiviral prophylaxis was modified based on insurance coverage or oral tolerability. GVHD prophylaxis consisted of PTCy (cyclophosphamide 50 mg/kg on days +3 and +4) with tacrolimus (target levels 5–15 mcg/L until day +100, with the goal of discontinuation by day +180) and mycophenolate mofetil 1 g every 8 h on days +5 to +35. Sirolimus, alemtuzumab or antithymocyte globulin were not used. All patients received filgrastim from day +5 until an absolute neutrophil count greater than 1000/mcL for two consecutive days. Patients on LET received acyclovir 800 mg PO twice daily for at least 1-year. Patients on HDV were changed to acyclovir once HDV was discontinued. Plasma CMV polymerase chain reaction (PCR) monitoring was conducted weekly day +10 throughout immune suppression. Patients with a low-positive CMV PCR (<400 IU/mL) on day +10 were included if the subsequent PCR result decreased while on prophylaxis and did not require antiviral treatment within seven days. CMV infections were treated with IV GCV or oral valganciclovir (vGCV). The CMV PCR threshold for antiviral treatment was not standardized and left to physician discretion. No institutional changes in antiviral treatment recommendations occurred during the period assessed. The institutional CMV testing methodology changed during the study period. Prior to 2018, an FDA-approved assay with a limit of detection (LOD) of 91 IU/mL and a linear range of 137–9,100,000 IU/mL was used. In 2018, the assay was changed to a different FDA-approved assay with an LOD of 35 IU/mL and a linear range of 35–10,000,000 IU/mL. During both periods, results were reported in IU/mL. No other significant systematic changes in supportive care occurred during the study period that would be expected to impact the incidence of CMV infection.

The primary endpoint was incidence of CMV infection, defined as a serum PCR ≥137 IU/mL (or <137 IU/mL if treated) by day +100. Secondary endpoints included the frequency of CMV antiviral treatment day +100, CMV infection and treatment by day +200 and by 1 year, CMV event-free survival (EFS), time to CMV infection, viral load at CMV infection and peak viral load, CMV treatment duration, incidence of CMV disease, peak peripheral blood (PB) eosinophil percentage during prophylaxis, time to neutrophil and platelet engraftment, as well as the incidence of acute (a) and chronic (c) GVHD, neutropenia and thrombocytopenia post engraftment, and relapse free and overall survival (OS) at 1-year. In the CMV EFS analysis, an event was defined as CMV infection, initiation of antiviral treatment, or death from any cause. aGVHD was graded by the Mount Sinai Acute GVHD International Consortium Criteria and assessed up to day +100 [22]. Neutrophil engraftment was defined as the first of three consecutive days of absolute neutrophil count >500/mm^3. Platelet engraftment was defined as the first of three consecutive days of platelets >20,000/mm^3. Severity of neutropenia and thrombocytopenia were graded using the common terminology criteria for adverse events (CTCAE) v5.0 [23]. All patients were followed for 1 year after alloHCT. Nominal data were analyzed using the Chi-square or Fisher's exact test. Non-parametric continuous data were analyzed using the Wilcoxon Rank Sum test. CMV EFS was calculated with death as a competing risk using a competing-risks regression and analyzed using Gray's test. Survival was estimated using the Kaplan–Meier method and analyzed using the Log Rank test. This study was approved by the institutional review board of the University of Pennsylvania.

Results

Between February 2013 and May 2020, 38 CMV seropositive patients underwent haplo or MMUD alloHCT with CMV prophylaxis; 19 with HDV and 19 with LET. Baseline characteristics were similar between the groups as shown in Table 1. MMUD alloHCTs were all one HLA antigen mismatches at the HLA-A, -B, -C, or DRB1 gene locus. Three patients in each group had a low positive CMV PCR on day +10, with three below the LOD. The median duration of prophylaxis was similar between the groups; HDV: 104 days, LET: 100 days.

Table 1. Patient characteristics.

Characteristic	HDV ($n = 19$)	LET ($n = 19$)	p value
Age, years, median (range)	64 (29–78)	64 (37–74)	.78
Male sex, *n* (%)	9 (47)	11 (58)	.52
Haploidentical transplant, *n* (%)	18 (95)	16 (84)	.29
Peripheral blood stem cells, *n* (%)	14 (74)	12 (63)	.73
Malignancy, *n* (%)			
AML	11 (58)	9 (47)	.52
Other	8 (42)	10 (53)	
Reduced intensity conditioning, % (*n*)	15 (79)	17 (89)	.37
Transplant CMV status			
Donor +/recipient +	8 (44)	9 (47)	.74
Donor −/recipient +	11 (58)	10 (53)	
Duration of prophylaxis, days, median (range)	104 (35–365)	100 (37–260)	.67
Duration of follow up, days, median (range)	365 (124–365)	365 (94–365)	.83

AML: acute myeloid leukemia.

Table 2. CMV outcomes.

Outcome	HDV ($n = 19$)	LET ($n = 19$)	p value RR or HR (95% CI)
CMV infection by d + 100, *n* (%)	10 (53)	1 (5)	.001 0.1 (0.14–0.71)
CMV infection requiring treatment by d + 100, *n* (%)	7 (37)	1 (5)	.017 0.14 (0.02–1.05)
CMV infection by d + 200, *n* (%)	11 (58)	4 (21)	.044 0.4 (0.15–1.05)
CMV infection requiring treatment by d + 200, *n* (%)	8 (42)	3 (16)	.074 0.38 (0.12–1.20)
CMV infection by 1 y, *n* (%)	11 (58)	4 (21)	.02 0.36 (0.14–0.94)
CMV infection requiring treatment by 1 y, *n* (%)	8 (42)	3 (16)	.074 0.38 (0.12–1.20)
CMV EFS (d), median (range)	80 (26–365)	NR	.024 HR 0.33 (0.12–0.86)
Time to CMV infection (d), median (range)	48 (26–105)	132 (64–143)	0.009
Viral load at infection (IU/mL), median (range)	392 (177–942)	184 (96–1460)	0.19
Peak CMV viral load (IU/mL), median (range)	559 (191–38,306)	638 (96–1460)	0.36
Duration of CMV treatment (d), median (range)	40 (14–80)	25 (24–40)	0.55

d: days; EFS: event-free survival; HR: hazard ratio; NR: not reached; RR: relative risk; y: year.

LET reduced the incidence of CMV infection by day +100 vs. HDV (5% vs. 53%, RR 0.01, 95% CI 0.014–0.71, $p = .001$) with a number needed to treat of two. LET also reduced the incidence of CMV infection requiring treatment by day +100 (5% vs. 37%, RR 0.14, 95% CI 0.18–0.99, $p = .017$). At both day +200 and 1-year post alloHCT, patients who received LET continued to have lower rates of CMV infection compared to those who received HDV, as shown in Table 2. No cases of CMV infection were observed in any of the four patients who underwent MMUD alloHCT.

With HDV, all CMV infections occurred while the patient was prescribed HDV, with no additional cases after discontinuation. With LET, three of four infections occurred while LET was prescribed, with viral loads of 172, 196, and 1460 IU/mL at infection. One additional patient had a viral load of 96 IU/mL after day +100, approximately 60 days after discontinuing LET, and was treated with GCV. Infection despite prophylaxis occurred later with LET than HDV (median 132 vs. 48 days, $p = .009$). Median CMV EFS was improved with LET vs. HDV (not reached vs. 80 days, HR 0.114, 95% CI 0.07–0.61, $p = .004$) as shown in Figure 1. No cases of CMV disease were observed in either group. All CMV infections responded to (v)GCV treatment. All patients with low detectable CMV viremia at the time of prophylaxis initiation became PCR negative; however, 2/3 receiving HDV developed CMV infection (all by day +100), while 0 of three patients receiving LET had CMV infection within 1-year.

Given the relationship between CMV and GVHD, we compared the incidence of GVHD between the groups. In addition, LET has been associated with increased PB eosinophils [24], also common in GVHD. Peak PB eosinophil percentages during prophylaxis were similar between the groups (HDV 11% (2–32.1%) vs. LET 10.8% (1.7–35.2%), $p = .83$). The time to neutrophil and platelet engraftment, incidences of grade 2–4 and 3–4 aGVHD, cGVHD, relapse at 1 year, and 1-year OS were similar between the groups, as shown in Table 3. Grade 3–4 post engraftment neutropenia was more

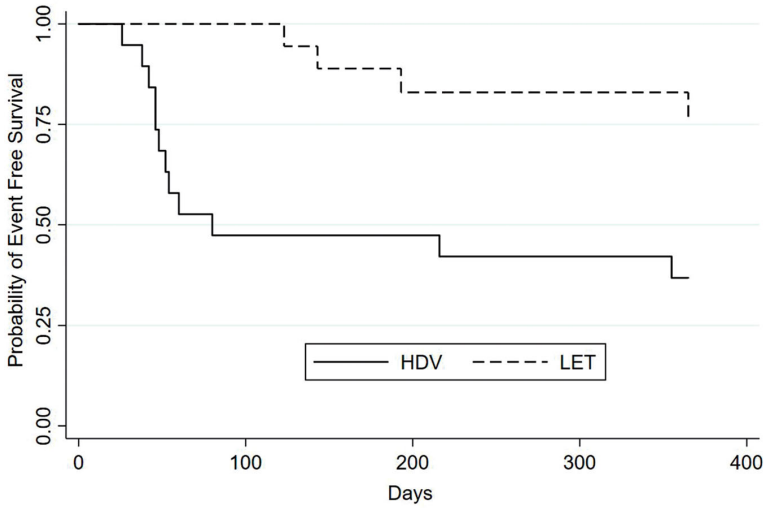

Figure 1. CMV event-free survival. LET vs. HDV: median not reached vs. 80 days, HR 0.114, 95% CI 0.07–0.61, p=.004.

Table 3. Transplant outcomes.

Outcome	HDV ($n = 19$)	LET ($n = 19$)	RR (95% CI) p value
Time to neutrophil engraftment, d, median (range)	18 (13–33)	20 (13–43)	0.45
Time to platelet engraftment, d, median (range)	20 (12–54)	25 (11–160)	0.55
Grade 2–4 neutropenia between engraftment and d + 100, *n* (%)	8 (42)	12 (63)	1.5 (0.8–2.8) .33
Grade 3–4 neutropenia between engraftment and d + 100, *n* (%)	3 (16)	9 (47)	3.0 (0.96–9.39) .079
Grade 2–4 thrombocytopenia between engraftment and d + 100, *n* (%)	10 (53)	13 (68)	1.3 (0.77–2.20) .51
Grade 3–4 thrombocytopenia between engraftment and d + 100, *n* (%)	6 (32)	7 (37)	1.17 (0.48–2.83) 1.0
Grade 2–4 aGVHD by d + 100, *n* (%)	5 (26)	5 (26)	1.0 (0.48–2.09) 1.0
Grade 3–4 aGVHD by d + 100, *n* (%)	1 (5)	2 (11)	2.0 (0.20–20.2) 1.0
Chronic GVHD by 1 year, *n* (%)	6 (32)	7 (37)	1.17 (0.48–2.83) 1.0
Relapse at 1 y, *n* (%)	5 (26)	4 (21)	0.80 (0.25–2.53) 1.0
Overall survival at 1 y, *n* (%)	13 (68)	15 (79)	1.15 (0.79–1.69) .71

aGVHD: acute graft-vs.-host disease; d: days.

common with LET than HDV; however, this did not reach statistical significance. There was no significant difference in relapse-free survival (HR 0.69, 95% CI 0.19–2.44, $p = .56$) or OS (HR 0.68, 95% CI 0.19–2.40, $p = .54$) between the groups, as shown in Figures 2 and 3. In the HDV group, four patients died of relapsed malignancy, one of infection, and one of multiorgan failure related to prior sepsis. In the LET group, two patients died of relapsed malignancy, one of infection, and one of multiorgan failure related to prior sepsis.

Discussion

In this retrospective single center study, we found LET was associated with a reduction in CMV infection at 100 days, 200 days, and 1 year following haplo alloHCT compared to HDV. No cases of CMV disease occurred. Prior to LET, various doses of valacyclovir were studied for CMV prophylaxis (Table 4). While HDV 2 g PO every 8 h has not been studied in haplo or MMUD alloHCT with PTCy, the incidence of CMV infection with HDV in umbilical cord blood (UCB) alloHCT [12,14] appears similar to our findings, suggesting HDV performed as expected. In the phase 3 trial of LET, starting at a median of day +9 and continued through day +100, csCMVi was reduced at weeks 14 and 24 vs. placebo. Outcomes were consistent between low risk and high risk populations, including haplo and MMUD alloHCT [16]. Subsequently, several real world experiences with LET have included haplo

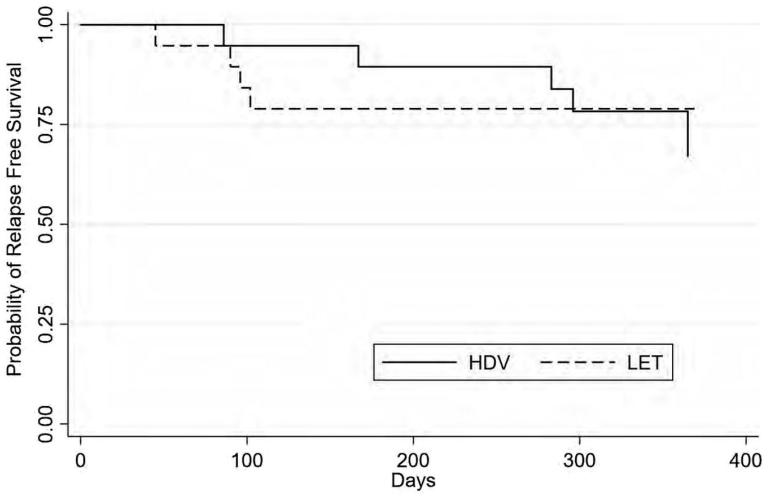

Figure 2. Relapse-free survival. HR 0.69, 95% CI 0.19–2.44, p=.56.

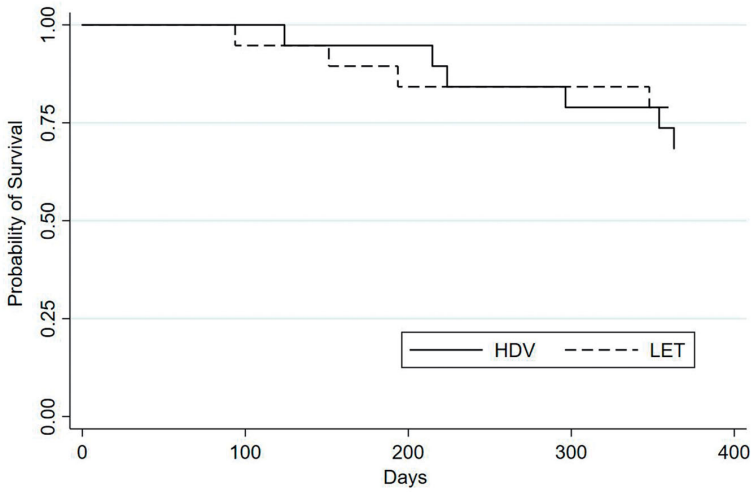

Figure 3. Overall survival. HR 0.68, 95% CI 0.19–2.40, p=.54.

and MMUD alloHCT. A single center study where approximately 75% of patients underwent haplo or MMUD alloHCT compared LET to preemptive therapy. csCMVi by day +100 occurred in 4% vs. 59% with preemptive therapy (p<.001), a frequency that mirrors our study, while using a similarly aggressive threshold for treatment (200 IU/mL) [27]. Another single center report compared LET to no prophylaxis in haplo and MMUD alloHCT with PTCy and observed a lower incidence of CMV infection requiring therapy by day +180 with LET (21.9% vs. 68.8%, p<.001). Importantly, the median duration of LET prophylaxis was 191 days in this study, exceeding the duration used in the phase 3 trial [18].

To our knowledge, the only published data comparing LET to an active control is a single center, retrospective comparison to HDV in UCB or haplo-cord blood alloHCT. This study reported a statistically insignificant reduction in CMV infection with LET vs. HDV (with or without pre-alloHCT GCV) by day +100 (22% vs. 33%, p = .21). Importantly, all CMV infections with LET had low level viremia, with a peak whole blood PCR value <1000 IU/mL and resolved without treatment (vs. 10% with HDV, p = .06) [28]. Comparisons to our study are difficult as PTCy was not used and the haplo-cord product may influence CMV risk.

The CMV treatment threshold was based on physician discretion, taking into consideration patient

Table 4. Literature summary of HDV prophylaxis following alloHCT.

Reference	Patient population, study design	Prophylaxis regimen	Incidence of CMV infection	Comments
Hammerstrom et al. [25]	Haplo alloHCT, retrospective, single center	GCV 5 mg/kg q12h from admission through d − 2, then vACV 500 mg PO daily d − 1 through +4, then vACV 1 g PO q8h d + 5 to d + 100	71% at 100 d	50% lower vACV dose than HDV group of the current study. Reduced incidence of CMV infection compared to vACV 500 mg daily d −1 through d + 100 (81%, p=.08).
Vusirikala et al. [26]	MUD/MRD alloHCT, retrospective, single center	vACV 1 g PO q8h (start day, duration not specified)	25% at a median follow-up 390 d	Haplo and MMUD alloHCT excluded, PTCy GVHD prophylaxis not used. Reduced incidence of CMV infection compared to ACV 400 mg PO twice daily (77%, p<.01).
Ljungman et al. [13]	MUD/MRD alloHCT, randomized, prospective, multicenter	vACV 2 g PO q6h	28%	Haplo alloHCT excluded. Limited enrollment of MMUD alloHCT (approximately 7% of study population). PTCy use not reported, likely limited due to period of study. 17% were CMV seronegative. Reduced incidence of CMV infection compared to ACV 800 mg PO q6h (40%, p<.0001).
Winston et al. [15]	Randomized, prospective, multicenter	vACV 2 g PO q6h	12%	Haplo alloHCT excluded. Limited enrollment of MMUD alloHCT (approximately 9% of study population). PTCy use not reported, likely limited due to period of study. Similar incidence of CMV infection compared to GCV prophylaxis (19%, p=.93).
Milano et al. [12]	UCB alloHCT	Pre alloHCT GCV followed by vACV 2 g PO q8h	60%	Reduced incidence of CMV infection compared to ACV 800 mg PO q12h or vACV 500 mg PO q12h (100%, p<.001). Subsequent study omitting GCV showed similar incidence of CMV infection compared to HDV alone [16].

ACV: acyclovir; GCV: ganciclovir; d: day; h: hour; q: every; PO: by mouth; UCB: umbilical cord blood; vACV: valacyclovir.

specific risk factors. Many authors cite a plasma CMV PCR of 1000 copies/mL as the threshold to initiate treatment [11,29]; however, the phase 3 LET trial treated at 150 copies/mL for high risk and 300 copies/mL for low risk patients [16]. Similar treatment thresholds have been recommended for high risk patients receiving LET [30]. A low treatment threshold may be prudent as a viral load of 250 IU/mL has been associated with increased non-relapse mortality [2] and a peak viral load of ≥150 IU/mL has been associated with a reduced probability of spontaneous clearance, albeit these data were reported prior to the availability of LET [31]. Had the threshold of 1000 IU/mL been required for treatment in this study, only four patients in the HDV and two patients in the LET group would have received treatment, a smaller and potentially insignificant difference, albeit viral load may have continued to increase in the absence of treatment. Furthermore, the clinical significance of low level CMV viremia on LET has been questioned as some viremia detected by PCR may be long, noninfectious DNA molecules that are released from abortively infected cells. Such noninfectious CMV viremia is more common in patients starting LET later (day +10) vs. earlier (day 0 or +1) and resolve without treatment [32]. Whether low level viremia developing after a longer duration of LET exposure similarly represents a noninfectious event remains unclear. In our series, the earliest infection on LET occurred 54 days following initiation. Such data may suggest that the antiviral treatment threshold for patients on LET may need revision in order to avoid overtreatment.

We identified four patients in the LET group that developed CMV infection; three occurred while the patient was prescribed LET, and all but one occurred after day +100. The mechanisms resulting in breakthrough viremia remain unclear. Resistance associated variants in the UL56 gene have been reported but are uncommon [33]. Breakthrough infections can occur without mutations, potentially related to malabsorption or poor adherence [34]. No patients in this cohort underwent sequencing to identify resistance associated variants. Few patients (6/38) had low level CMV viremia (<400 IU/mL) at the time of prophylaxis initiation, a common scenario in haplo alloHCT [34], which has been postulated to contribute to prophylaxis failure [18,33]. We decided to include these patients given a post hoc analysis of patients with detectable CMV DNA at randomization in the phase 3 trial showed similar outcomes to those without detectable CMV [35]. Subsequent real world analyses have also reported successful prevention of CMV infection in a limited number of patients with detectable viremia prior to starting LET [18,27].

We analyzed both haplo (n = 34) and MMUD (n = 4) alloHCT together assuming PTCy was the primary CMV

risk factor; however, differences in donor, stem cell source, or GVHD prophylaxis may also be important risk factors. A recent large, retrospective CIBMTR analysis observed an approximately twofold increased risk (and approximately 40% incidence) of CMV infection in both haplo ($n = 757$) and matched-related donor (MRD) alloHCT ($n = 403$) who received PTCy compared to MRD alloHCT with calcineurin-inhibitor-based GVHD prophylaxis without PTCy. In this study, roughly 2/3 of patients received PB stem cells and no use of sirolimus was reported [3]. In contrast, a recent small ($n = 80$) prospective CIBMTR study of MMUD bone marrow (BM) transplants receiving PTCy, sirolimus, and MMF GVHD prophylaxis observed a much lower grade $\geq$2 CMV infection incidence of $\leq$11% [36]. Furthermore, in a single center retrospective study ($n = 22$ PTCy MMUD and $n = 19$ PTCy haplo alloHCT) where roughly 90% of patients received PB stem cells, patients undergoing PTCy MMUD alloHCT had a lower incidence of csCMVi compared to haplo alloHCT at 200 days (25 vs. 53%, $p = .03$). The difference remained significant after adjustment for LET (OR 0.23, 95% CI 0.07–0.81, $p = .02$), which was more commonly used following MMUD (45%) vs. haplo (16%) alloHCT. Sirolimus GVHD prophylaxis was also more commonly used following MMUD vs. haplo alloHCT [37], which has previously been reported to be protective against CMV infection [38]. Taken together, it is unclear if these divergent findings are due to differences in the stem cell source, use of sirolimus vs. tacrolimus, differences in CMV-specific immune reconstitution, or other patient or transplant characteristics and highlight the need for further study to characterize the risk of CMV infection in patients undergoing MMUD alloHCT with PTCy.

Our study has limitations based on its retrospective design. We were only able to include a modest number of patients in each group. While LET was compared to an active historical control, patient characteristics were similar between the groups. While selection bias was unlikely, it is possible that other poorly defined practice changes over time could have impacted outcomes. However, published literature describing LET prophylaxis in this population at present is limited, and as such, reports of even limited sample size with historical comparisons can represent an important contribution. Use of both haplo alloHCT and MMUD alloHCT with PTCy are becoming more frequent transplant approaches. Based on these favorable outcomes, no further patients will be prescribed HDV, thus limiting the size of the control arm. The duration of follow-up was relatively short, limited to 1 year in both groups to allow equal follow-up, given the more recent use of LET. Longer follow-up past 1 year is unlikely to significantly change CMV infection outcomes as both groups terminated prophylaxis roughly at day +100; however, other outcomes such as relapse or GVHD could be impacted. We are also unable to comment on patient compliance to prescribed prophylaxis given the retrospective nature of this analysis. Lastly, financial implications of LET vs. HDV prophylaxis were not assessed in this study yet remain important considerations. The LET acquisition cost is significantly greater than HDV; however, the reduction in CMV infection and resultant costs of therapeutic antivirals, hospitalization, and additional supportive care may make LET prophylaxis cost effective in high risk patients and should be assessed in future studies.

Conclusions

LET was associated with a reduced incidence of CMV infection and need for antiviral treatment by day +100, +200, and 1 year following haplo alloHCT receiving PTCy. LET was also associated with improved CMV EFS vs. HDV without any detrimental effects on transplant outcomes. While prospective studies are required to definitively validate our results, we believe that this study combined with available published data support the routine use of LET in recipients of haplo or MMUD alloHCT who receive PTCy GVHD prophylaxis.

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